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Articles

7E3 Monoclonal Antibody Directed Against the Platelet Glycoprotein IIb/IIIa Cross-reacts With the Leukocyte Integrin Mac-1 and Blocks Adhesion to Fibrinogen and ICAM-1

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Abstract

- Top
- Abstract
- Introduction
- Methods
- Results
- Discussion
- References

Abstract Recent clinical trials suggest that blockade of integrins is a promising strategy for the treatment of acute coronary syndromes. Administration of 7E3 monoclonal antibody (mAb) Fab fragment (c7E3 Fab) directed against platelet integrin IIb/IIIa (αIIbβ3, CD41/CD61) reduces acute ischemic complications of coronary angioplasty and clinical restenosis at 6 months. However, 7E3 mAb is not selective for platelet IIb/IIIa but also cross-reacts with the leukocyte integrin Mac-1 (αMβ2, CD11b/CD18) and the vitronectin receptor (αvβ3, CD51/CD61). Information regarding how this mAb may affect other cells important in vascular repair is scant. Potential interactions of c7E3 Fab with inflammatory (ie, monocytes and neutrophils), vascular smooth muscle, and endothelial cells may contribute to the in vivo actions of c7E3 Fab. In this study we explored the binding of 7E3 to monocytic cells and the functional effect of 7E3 and c7E3 Fab on Mac-1–mediated adhesion to fibrinogen (FGN) and intercellular adhesion molecule-1 (ICAM-1), ligands abundant in the injured vessel wall. Flow cytometry demonstrated that 7E3 bound to THP-1 monocytic cells and identified a subpopulation ($\approx$10%) of Mac-1 that was qualitatively similar to that recognized by CBRM1/5, a mAb directed to an activation-specific neoepitope present on a subset of Mac-1 molecules. mAb 7E3 bound to K562 cells transfected with just the α subunit (CD11b) of Mac-1 but not to nontransfected cells, confirming a direct interaction between 7E3 and Mac-1. mAb 7E3 and c7E3 Fab blocked the adhesion of Mac-1–bearing cells to FGN (80±11% and 78±9% inhibition, respectively) and ICAM-1 (62±14% and 62±17%). Both 7E3 and c7E3 Fab significantly inhibited (70±6% and 62±26%)

soluble FGN binding to human peripheral blood monocytes. Thus, c7E3 Fab cross-reacts with the CD11b subunit of Mac-1 and interrupts cell-extracellular matrix and cell-cell adhesive interactions and may thereby influence the recruitment of circulating monocytes to sites of vessel injury. Given the recent evidence that adherent and infiltrating monocyte number directly correlates with the extent of neointimal hyperplasia, inhibition of Mac-1–dependent adhesion and IIb/IIIa-dependent function by c7E3 Fab may jointly contribute to the regulation of vascular repair and to the sustained clinical benefits observed with c7E3 Fab after angioplasty.

Key Words: integrins • monocytes • cellular adhesion • restenosis • monoclonal antibody

Introduction

▲ Top
▲ Abstract
· Introduction
▼ Methods
▼ Results
▼ Discussion
▼ References

Restenosis is the major limitation of all percutaneous coronary revascularization procedures, leading to recurrent anginal symptoms and repeat interventions in up to 40% of patients within 6 months.[1] [2] [3] Restenosis is the arterial healing response to vascular injury, characterized pathologically by vessel elastic recoil, thrombus formation/incorporation, and neointimal hyperplasia secondary to smooth muscle cell proliferation and migration and excessive extracellular matrix production.[4] [5] [6] [7] [8] Although various drugs (eg, heparin and angiotensin-converting enzyme inhibitors) have been successful in reducing neointimal thickening in animal models of restenosis,[9] no agent has proved to be effective in large-scale clinical trials.[10] Recently, however, the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial has demonstrated that bolus and 12-hour infusion of a murine/human chimeric 7E3 mAb fragment (c7E3 Fab) directed against the platelet integrin IIb/IIIa not only reduced acute ischemic complications of coronary angioplasty by 35%,[11] an effect attributed primarily to the ability of c7E3 Fab to potently inhibit platelet aggregation by blocking platelet fibrinogen binding, but also reduced clinical restenosis—major ischemic events and the need for repeat revascularization procedures—at 6 months by 23%.[12] The sustained benefit of c7E3 Fab has been attributed to its inhibitory effect on IIb/IIIa and to vessel wall "passivation," a process by which the vascular response to injury is attenuated through poorly characterized effects on cells and extracellular matrix of the vessel wall.

Receptors of the integrin family are an important class of cell adhesion molecules that mediate cell-cell and cell–extracellular matrix interactions that are central to inflammation, wound healing, and hemostasis.[13] Since integrins share common α and ß subunits and because there is a high degree of homology between subunit families,[14] it is not surprising that some mAbs bind to more than one integrin. c7E3 Fab is not selective for platelet IIb/IIIa (αIIbß3, CD41/CD61) but also cross-reacts with the vitronectin receptor (αvß3, CD51/CD61),[15] found on endothelial and smooth muscle cells, and the integrin Mac-1 (αMß2, CD11b/CD18),[16] found on monocytes and neutrophils.

Mac-1, a leukocyte integrin that is mobilized from intracellular storage pools in response to a variety of agonists, including ADP, C5a, fMLP, and phorbol esters,[17] [18] is capable of binding heterogeneous ligands including ICAM-1,[19] fibrin(ogen),[20] [21] [22] and factor X.[23] The binding of Mac-1 to ICAM-1 and

fibrin(ogen) results in the adhesion of neutrophils/monocytes to the endothelium and to sites of fibrin deposition, respectively. After binding to factor X, Mac-1 coordinates the activation of factor X independent of tissue factor and factor VII, culminating in rapid fibrin formation.[23] mAbs to Mac-1 interrupt the adhesive and migratory capability of leukocytes and reduce tissue injury in models of inflammation.[24] [25] [26] [27]

Circulating monocytes are among the earliest cells recruited to sites of vessel injury[28] [29] and have the potential to interact with other vascular cells by secreting growth factors and cytokines.[30] [31] [32] In fact, adherent and infiltrating monocyte number directly correlates with the extent of neointimal hyperplasia after deep vessel injury.[33] Our demonstration in this study that 7E3 and c7E3 Fab inhibit Mac-1–mediated adhesion to FGN and ICAM-1 in vitro may provide an additional mechanism for the beneficial effects of this mAb therapy.

Methods

Top
Abstract
Introduction
Methods
Results
Discussion
References

Materials

ADP and the chemotactic peptide fMLP were purchased from Sigma Chemical Company. Human plasminogen-free FGN was purchased from Enzyme Research Laboratories. FGN was iodinated with Iodobeads as previously described.[34] TGF-ß1 was from Collaborative Research Inc, and 1,25-$(OH)_2$ vitamin D_3 was a gift of Dr M. Uskokvic (Hoffman-LaRoche Laboratories, Nutley, NJ). LPM19c, a mAb to the αM subunit of Mac-1 (CD11b) that blocks FGN binding to Mac-1,[35] was purchased from DAKO Corp. The stimulating CD18 mAb KIM127 was a generous gift of Dr Martyn Robinson (Celltech Ltd, Slough, England).[36] Additional Mac-1 mAbs included TS1/18, a mAb to the common ß2 subunit (CD18) of Mac-1, and CBRM1/5, a mAb to an activation-specific neoepitope in a subpopulation of Mac-1 molecules (kindly provided by Dr Timothy A. Springer, Harvard Medical School, Boston, Mass).[37] mAbs 7E3 and 10E5,[38] murine mAbs to glycoprotein IIb and/or IIIa that block platelet FGN binding, and c7E3 Fab,[39] a Fab fragment of a human-mouse genetic reconstruction of murine 7E3, in which mouse heavy and light chain variable regions were linked to the constant domains of a human IgG1 heavy chain and κ light chain, respectively, were kindly provided by Dr Barry S. Coller (Mt Sinai Medical Center, New York, NY). Soluble human ICAM-1/Ig, a recombinant fusion protein comprising the extracellular domain of human ICAM-1 linked to the constant region of human IgG1, was obtained from Chiron Corp. FITC-conjugated goat anti-mouse IgG, $F(ab')_2$ antibody was obtained from Boehringer Mannheim Corp.

Cell Transfection

Erythroleukemic K562 cells (European Collection of Animal Cell Cultures) were transfected with the αM (CD11b) subunit of Mac-1 as previously described.[40] The CD11b gene was cloned by PCR amplification from first-strand cDNA prepared from U937 cells stimulated with 10 ng/mL phorbol myristate acetate for 48 hours. The gene was cloned into the expression vector EE6 hCMV carrying a G418-resistance marker for expression in K562 cells. This plasmid was linearized by using *Sal* I and then 40 μg of linearized DNA was transfected into 10^7 K562 cells by electroporation, using a BioRad Gene Pulser unit. Cells and DNA were subjected to one pulse at 250 V with a capacitance of 900 μF.

CHO cells transfected with human Mac-1 (CD11b/CD18) or the closely related leukocyte integrin p150,95 (CD11c/CD18) were provided by Dr Timothy A. Springer.[35] Briefly, αM (CD11b) or αX (CD11c) and ß2 (CD18) subunits of Mac-1 in pCDM8 were cotransfected by electroporation with the pDCHIP plasmid, containing a CHO dihydrofolate reductase minigene, into CHO DG44 cells. Cells were selected with methotrexate, and a homogeneous population of positively expressing cells was obtained by immunopanning. Expression was then augmented by increasing the concentration of methotrexate (0.05 to 0.2 μmol/L) in culture. Both types of transfected cells, but not the nontransfected DG44 cells, acquired the ability to bind soluble ^{125}I-labeled FGN. Furthermore, Mac-1 and p150,95 transfectants bound equivalent amounts of ^{125}I-FGN, confirming equivalent expression of functional protein.

Cell Lines and Culture Conditions

The monocytic THP-1 cell line (American Type Culture Collection) was maintained in RPMI 1640 and supplemented with 10% (vol/vol) FBS. Unless otherwise indicated, medium containing 20 mmol/L HEPES, 2 mmol/L L-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin was used in all cases. Differentiation of monocytic cells (10^6 per milliliter), which is accompanied by increased expression of Mac-1, was induced by treatment with 1 ng/mL TGF-ß1 and 50 nmol/L 1,2-$(OH)_2$ vitamin D_3 for 24 hours.[41] K562 cells were cultured in DMEM supplemented with 10% FBS; CD11b K562 cells were cultured in DMEM containing G418 (1 mg/mL) and 10% FBS. Mac-1 and p150,95 CHO cells were cultured in α-MEM supplemented with 10% heat-inactivated, dialyzed FBS, 0.1 μmol/L methotrexate, and 10 μmol/L thymidine. Incubations were performed at 37°C, 5% CO_2. Peripheral blood mononuclear cells were isolated from 10% (vol/vol) CPD-anticoagulated human blood by Ficoll-Hypaque centrifugation[42] and human monocytes were separated from peripheral blood mononuclear cells by adherence to human AB serum-coated plastic Petri dishes. Monocytes were maintained in RPMI 1640 supplemented to 10% (vol/vol) with human AB serum.

Adhesion Assays

Adherent cells were assayed by a colorimetric method, as previously described.[43] [44] Cytokine-primed monocytic THP-1 cells or Mac-1–transfected CHO cells were activated with ADP (10 μmol/L), fMLP (1 μmol/L), or the Mac-1–activating mAb KIM 127 (10 μg/mL). Activated cells were then added to wells precoated with the Mac-1 ligands FGN (100 μg/mL) or ICAM-1 (10 μg/mL) and blocked with gelatin. Cells (10^5 per well) were resuspended in serum-free RPMI containing 0.5% BSA at 10^6 per milliliter and were incubated in the presence or absence of the indicated mAbs (intact 7E3, c7E3 Fab, 10E5 [anti-IIb/IIIa, non–cross-reacting with Mac-1],[45] and LPM19c [anti-CD11b]) at a concentration of 1 to 20 μg/mL and placed in 96-well microtiter plates for 1 to 2 hours at 37°C. Plates were washed with 0.9% NaCl three times, and adherent cells were fixed in methanol for 15 minutes, stained with Giemsa, and adhesion-quantified by measuring absorbance at 540 nm. Data are expressed as percent of maximum adherent responses of respective sets of treatment.

Flow Cytometry

K562 or THP-1 cells ($2.5x10^6$ per milliliter) were washed and resuspended in 200 μL of RPMI containing 2.5% BSA. Fc receptors were blocked by addition of human serum at a final concentration of 1%. The primary mAb was then added to the cell suspension followed by incubation on ice for 30 minutes. Cells

were treated with ADP (10 μmol/L) or fMLP (1 μmol/L) for 15 minutes at 37°C before incubation with the primary mAb. After washing, cells were resuspended in 200 μL of the same medium containing FITC-conjugated goat anti-mouse $F(ab')_2$ fragments and incubated for 30 minutes on ice. Flow cytometry was performed on a Becton Dickinson FACScan (Becton Dickinson Immunocytometry Systems). Excitation wavelength was set at 488 nm and emission at 550 nm. Nonspecific fluorescence was determined on cells incubated in the absence of the primary mAb.

Fibrinogen Binding Assay

The binding of soluble FGN to human peripheral blood monocytes was investigated as previously described by Altieri and coworkers[20] with modification. ^{125}I-labeled FGN (1.0 μmol/L) was added to ADP-stimulated human monocytes (10^5) adherent to microtiter wells for 60 minutes at 25°C. Cell-free FGN was removed by washing the adherent human monocytes, and cell-bound FGN was determined by counting an aliquot of the cell lysate. Specific binding was calculated by subtracting the counts obtained in the presence of a 20-fold excess of unlabeled FGN from total binding. The effect of mAbs was determined by preincubating ADP-stimulated monocytes for 30 minutes before the addition of ^{125}I-FGN.

Results

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
• Results
▼ Discussion
▼ References

Interaction of 7E3 With Myelomonocytic Cells

The ability of 7E3 to interact with monocytic cells was first explored by using flow cytometry. Prior reports that 7E3 cross-reacts with Mac-1 on blood monocytes have been cautiously interpreted due to concerns about potential platelet contamination. To exclude the possibility that the responses of monocytes would be influenced by platelet contamination, we have used a monocytic (THP-1) cell line and cell lines (K562 and CHO cells) transfected with human Mac-1. Integrin receptors require regulated and reversible activation, which can be induced by ligand binding and by cellular stimulation with a variety of agonists (eg, ADP, fMLP).[46,47] Reporter mAbs are capable of defining this high-affinity or activated state. A small subpopulation of Mac-1, representing 10% to 20% of total Mac-1, is recognized by mAb CBRM1/5.[37] CBRM1/5 is directed to an activation-specific neoepitope on Mac-1 and is capable of completely blocking Mac-1–dependent adhesion to FGN or ICAM-1. In contrast, LPM19c, a mAb to the αM subunit (CD11b) of Mac-1 that also blocks adhesion to FGN and ICAM-1,[35] recognizes total Mac-1 expressed. In accordance with the findings of Diamond and Springer[37] with neutrophils and monocytes, CBRM1/5 bound to fMLP activated THP-1 cells at a significantly lower level than LPM19c (mean fluorescence 49 versus 207; Fig 1A⊡). The fraction of Mac-1–bearing cells displaying the activation epitope recognized by CBRM1/5 ranged from 6% to 24% in THP-1 cells activated with fMLP or ADP. Similar to CBRM1/5, 7E3 bound fMLP-activated THP-1 cells at a lower level than LPM19c (mean fluorescence 19 versus 207; Fig 1A⊡). We further examined whether CBRM1/5 and 7E3 recognize distinct epitopes on activated THP-1 monocytic cells. Because c7E3 Fab is a humanized fragment of 7E3 that is not recognized by the FITC-conjugated anti-mouse antibody used in our flow cytometry experiments, we were able to address this question using flow cytometry. c7E3 Fab failed to block CBRM1/5 binding (data not shown), suggesting that these mAbs recognize distinct epitopes.

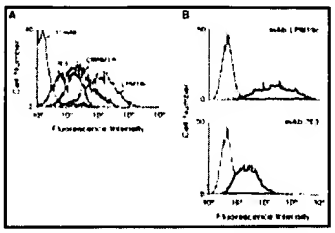

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Figure 1. Interaction of 7E3 antibody with THP-1 and K562 myelomonocytic cells. Binding of 7E3 to THP-1, K562, and CD11b K562 cells was analyzed using immunofluorescence flow cytometry as described in "Methods." Cytokine-primed THP-1 cells were stimulated with fMLP (1 μmol/L) and incubated with the following primary mAbs: LPM19c (anti-CD11b), CBRM1/5 (directed to an activation-specific neoepitope on CD11b), or 7E3. Deletion of primary antibody served as the negative control (A). K562 (unshaded) and CD11b K562 (shaded) cells were stimulated with fMLP and incubated with LPM19c or 7E3 (B). The abscissa represents fluorescence intensity; the ordinate, cell number.

To determine whether 7E3 bound directly to Mac-1 on monocytic cells, we used erythroleukemic K562 cells, which do not express Mac-1 and are capable of being stably transfected.[40] 7E3 bound to K562 cells transfected with the α subunit (CD11b) of Mac-1 but not to nontransfected cells, supporting a direct interaction between 7E3 and Mac-1 (Fig 1B).

7E3 and c7E3 Fab Antibodies Inhibit Mac-1–Mediated Adhesion to FGN and ICAM-1

The functional relevance of 7E3's cross-reaction with Mac-1 was investigated by exploring the effect of 7E3 or c7E3 Fab on cellular adhesion to FGN and ICAM-1. The agonist fMLP increased adhesion of monocytic THP-1 cells to FGN-coated wells >10-fold (Fig 2A and 2B). LPM19c, an anti-CD11b mAb that blocks FGN binding to Mac-1,[35] inhibited FGN adhesion by 82% ($P<.01$), indicating that THP-1 cell adhesion is Mac-1 dependent. 7E3 and c7E3 Fab blocked adhesion to FGN by 80% and 78% ($P<.01$), respectively. 10E5, an anti-IIb/IIIa mAb that does not cross-react with Mac-1,[45] had minimal effect. A dose response for the inhibition of monocytic cell adhesion by 7E3 is depicted (Fig 2C), indicating that the IC_{50} is ≈10 μg/mL.

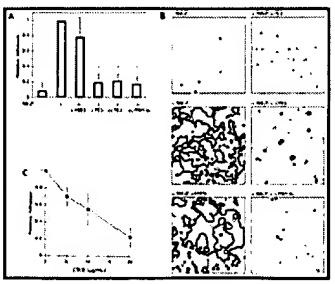

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Figure 2. Inhibition of THP-1 monocytic cell adhesion to fibrinogen by 7E3 and anti-CD11b antibodies. The effect of 7E3/c7E3 Fab and anti-CD11b (LPM19c) on Mac-1–mediated adhesion to FGN-coated microtiter wells was investigated in THP-1 monocytic cells. TGF-ß1/1,2-$(OH)_2$ vitamin D_3 THP-1 cells were stimulated with fMLP (1 μmol/L), incubated with 7E3, c7E3 Fab, LPM19c, or control (10E5) mAbs (20 μg/mL), and then added to FGN-coated wells for 2 hours at 37°C. Adherent cells were fixed and stained for quantification (A) or photography (B). Adhesion is expressed relative to adhesion stimulated by fMLP in the absence of mAb treatment. A dose response for inhibition by 7E3 (0 to 20 μg/mL) is depicted (C). Values represent mean±SD (n=3); *$P<.01$.

To confirm the ability of 7E3 to inhibit Mac-1 function and establish that inhibition by 7E3 or c7E3 Fab required Mac-1 expression, we also investigated CHO cells transfected with human Mac-1. CHO cells, which are devoid of Fc receptors, were selected for these experiments because our soluble ICAM-1 preparation is a recombinant fusion protein comprising the extracellular domain of ICAM-1 linked to the

constant region of human IgG1. Mac-1 CHO cells adhered to FGN after activation with the KIM 127 mAb (Fig 3). Adhesion by Mac-1 CHO cells was inhibited by LPM19c (95±2% inhibition), confirming the role of Mac-1 in this adhesive pathway. Further evidence that Mac-1 expression is necessary to promote the adhesion of CHO cells to FGN is supported by lack of demonstrable adhesion, under these conditions, of nontransfected DG44 CHO cells (data not shown) and CHO cells transfected with a distinct but closely related ß2 integrin, p150,95 (CD11c/CD18) (Fig 3). While p150,95 has been shown to mediate adhesion of fMLP-activated neutrophils[48] and phorbol ester–activated B lymphocytes[49] to FGN-coated surfaces, we were unable to demonstrate significant adhesion of KIM 127–stimulated p150,95 CHO cells to FGN in this experimental system. This lack of adhesion of p150,95 CHO cells may reflect cell-type–specific differences (transfected versus nontransfected cells) or different activation requirements in transfected cells.

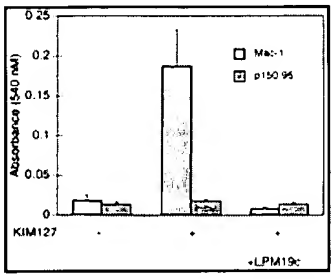

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Figure 3. Adhesion to FGN of CHO cells transfected with human Mac-1 (CD11b/CD18) or p150,95 (CD11c/CD18). The ability of CHO cells transfected with human Mac-1 (Mac-1 CHO) or p150,95 (p150,95 CHO) to adhere to FGN-coated wells was examined as outlined in "Methods." CHO cells were stimulated with KIM 127 (10 µg/mL), incubated with LPM19c mAb (20 µg/mL), and then added to FGN-coated wells for 2 hours at 37°C. Adherent cells were washed, fixed, and stained with Giemsa for quantification. Values represent mean±SD (n=3).

We next tested whether 7E3 would inhibit Mac-1 binding to ICAM-1, an adhesion molecule that facilitates the adhesion of monocytes and neutrophils to the endothelium.[19] KIM 127 stimulated adhesion of Mac-1 CHO cells to ICAM-1 (Fig 4A and 4B). LPM19c blocked adhesion to ICAM-1 by 86% ($P<.01$), indicating that transfected CHO cell adhesion to ICAM-1 is Mac-1 dependent. 7E3 and c7E3 Fab reduced adhesion to ICAM-1 by 62% and 63%, respectively ($P<.05$), while 10E5 had no effect.

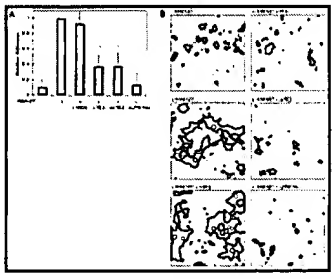

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Figure 4. Inhibition of Mac-1 CHO cell adhesion to ICAM-1 by 7E3 and anti-CD11b antibodies. The effect of 7E3/c7E3 Fab and anti-CD11b (LPM19c) on adhesion to ICAM-1–coated microtiter wells was investigated in Mac-1 CHO cells. Mac-1 CHO cells were stimulated with KIM 127 (10 µg/mL), incubated with 7E3, c7E3 Fab, LPM19c, or control (10E5) mAbs (20 µg/mL) and then added to ICAM-1–coated wells for 2 hours at 37°C. Adherent cells were fixed and stained for quantification (A) or photography (B). Adhesion is expressed relative to adhesion stimulated by KIM 127 in the absence of mAb treatment. Values represent mean±SD (n=3); *$P<.05$.

7E3 and c7E3 Fab Antibodies Inhibit Mac-1–Mediated Soluble FGN Binding by Human Peripheral Blood Monocytes

To further evaluate the functional relevance of the interaction between 7E3 and Mac-1, we investigated whether 7E3 and c7E3 Fab are capable of modulating Mac-1 function in freshly isolated human peripheral blood monocytes. ADP-stimulated human monocytes bound soluble FGN (≈175 000 FGN molecules per cell). LPM19c inhibited FGN binding to human monocytes by 93% (Table), confirming that FGN binding to human monocytes is Mac-1 dependent. Both 7E3 and c7E3 Fab significantly inhibited soluble FGN binding to human peripheral blood monocytes. Lack of inhibition of FGN binding by 10E5, an anti-IIb/IIIa mAb that blocks FGN binding to IIb/IIIa but not to Mac-1,[45] not only confirms the specificity of 7E3 but also suggests that platelet contamination of peripheral blood monocytes is unlikely to account for soluble FGN binding to human monocytes.

View this table: [in this window] [in a new window]

Table 1. Inhibition of Soluble Fibrinogen Binding to Human Peripheral Blood Monocytes by 7E3

Discussion

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▲ Results
• Discussion
▼ References

This study demonstrates that c7E3 Fab or 7E3 directed against platelet IIb/IIIa also binds to Mac-1–expressing monocytic and transfected cells and thereby inhibits Mac-1–dependent adhesion to fibrin(ogen) and ICAM-1. mAbs that cross-react with multiple integrins have been described. Those reported include mAb 25E11, which cross-reacts with platelet IIb/IIIa and monocyte Mac-1,[50] and mAb 24, which detects an epitope within the cation binding domain common to the α subunit of the leukocyte integrins LFA-1 (CD11a), Mac-1 (CD11b), and p150,95 (CD11c).[51] Altieri and Edgington[16] have previously shown that 7E3 cross-reacts with monocyte Mac-1, recognizing an activation-dependent neoepitope induced by agonists such as ADP and fMLP, which induce transients in cytosolic Ca^{2+}. However, reports that 7E3 cross-reacts with Mac-1 have been cautiously interpreted owing to concerns about potential platelet contamination.[39] We have addressed this concern by using a monocytic cell line and cells transfected with human Mac-1. 7E3 bound to K562 cells transfected with the α subunit (CD11b) of Mac-1 but not to nontransfected cells, supporting a direct interaction between 7E3 and Mac-1. The demonstration of 7E3 binding to purified ligand binding or I domain of CD11b reported previously by Zhou and colleagues[52] provides additional compelling evidence for a direct interaction between 7E3 and Mac-1. These prior studies have explored the functional consequence of the cross-reaction of 7E3 with Mac-1 by examining soluble ligand (ie, factor X) binding, which was largely inhibited by 7E3 (75% to 88%).[16] The current study now shows that 7E3 blocks Mac-1–dependent adhesion to fibrin(ogen) and ICAM-1, ligands abundant in the acutely injured vessel wall.[53] A dose response for the inhibition of monocytic cell adhesion by 7E3 demonstrated an IC_{50} of ≈10 μg/mL (67 nmol/L). This is in close agreement with the reported K_d (≈150 nmol/L) of 7E3 for binding to Mac-1–bearing monocytes.[16] It is important to note that 7E3 apparently binds to Mac-1 with lower affinity than IIb/IIIa (K_d, 3.4 nmol/L).[38] Pharmacokinetic data indicate that bolus infusion of c7E3 Fab in cynomolgus monkeys resulted in a peak plasma concentration of

≈2.5 μg/mL (54 nmol/L, assuming molecular weight of c7E3 Fab of 48 kD).[39] Thus, the relative importance of 7E3-mediated inhibition of IIb/IIIa versus Mac-1 in vivo is currently unknown.

The avidity of integrins may be rapidly and reversibly altered from a latent ("inactive") state to a high-affinity ("active") state without changes in receptor number. Receptor activation, most likely secondary to conformational change(s), increases ligand affinity of ß1,[54] ß2,[36] and ß3[55] integrins. For example, agonist stimulation of platelets induces fibrinogen binding to activated IIb/IIIa that is blocked by mAb 7E3.[38] Coller and coworkers[38] have demonstrated that 7E3 recognizes an activation-dependent change in the conformation of IIb/IIIa, because resting platelets bind 7E3 more slowly than stimulated platelets. In the case of Mac-1, specific agonists (eg, ADP, fMLP) stimulating mAbs (eg, KIM 127 and 185)[36] [56] and Mn^{2+}[57] are capable of directly activating Mac-1 from a low- to high-affinity ligand-binding state by inducing Ca^{2+} transients or by binding to the ß2 subunit or divalent-cation domains of the αM subunit, respectively. Analagous to the interaction between 7E3 and platelet IIb/IIIa, CBRM1/5 is directed to an activation-specific epitope on leukocyte Mac-1 and is capable of completely blocking Mac-1–dependent adhesion.[37] Our data suggest the possibility that 7E3 also binds to activated Mac-1. 7E3 bound to CD11b K562 cells but not nontransfected K562 cells and identified a subpopulation of Mac-1 by flow cytometry that is qualitatively similar to the subpopulation identified by CBRM1/5. However, these mAbs apparently recognize distinct activation epitopes, because c7E3 Fab, a humanized Fab fragment of intact 7E3, failed to block CBRM1/5 binding as assessed by flow cytometry.

The early response to vascular injury is characterized by migration of platelets and inflammatory cells, including monocytes, to the injured vessel wall.[58] [59] Therefore, the ability of 7E3 to inhibit not only IIb/IIIa-mediated platelet aggregation but also Mac-1–mediated monocyte adhesion may contribute to the process of vessel wall passivation observed clinically in the EPIC Trial. Among the earliest cells recruited into experimental vascular lesions induced in animals and spontaneous atherosclerosis in human arteries,[28] [29] monocytes serve as markers, initiators, and promoters of vascular injury. Balloon injury of the vessel wall is associated with a marked increase in the expression and secretion of monocyte chemoattractant protein-1.[60] Pathological examination of human arteries and saphenous veins after angioplasty or stent placement has revealed monocytes adherent to and within vessel walls.[61] There is emerging evidence implicating infiltrating monocytes in the pathogenesis of neointimal hyperplasia after mechanical arterial injury. The activation status of circulating monocytes[62] and expression of Mac-1[63] at the time of angioplasty have been reported to predict later restenosis, and recently, Rogers and coworkers[33] have demonstrated that the number of adherent and infiltrating monocytes exquisitely correlated with the extent of neointimal thickening and proliferation after arterial injury. Libby and coworkers[7] have proposed a cascade model for restenosis, in which local inflammatory activation of endothelial cells, smooth muscle cells, and leukocytes occurs in a predictable sequence driven by ongoing autocrine and paracrine signals that persist after the original injury and contribute to later phases of intimal thickening. The precise mechanisms underlying the linkage between monocyte adhesion/infiltration and neointimal hyperplasia in this cascade model remain to be elucidated but may involve the elaboration of cytokines and growth factors chemotactic and mitogenic for smooth muscle cells.[30] [31] [32]

Therefore, we speculate that the cross-reaction of 7E3 or c7E3 Fab with Mac-1 may play an additional role in inducing passivity of the vessel wall by two mechanisms: (1) blocking the adhesion of monocytes to

ICAM-1 and fibrin(ogen) and (2) decreasing thrombus deposition at the site of arterial injury by inhibiting the binding of factor X and its activation to factor Xa, as previously shown by Altieri and coworkers.[23] Other platelet IIb/IIIa receptor inhibitors under active clinical investigation (ie, lamifiban, tirofiban, and xemlofiban) have varying degrees of specificity with the target (ie, IIb/IIIa) and homologous (ie, $\alpha v\beta 3$, Mac-1) integrins.[64] The clinical relevance of variable IIb/IIIa, Mac-1, and $\alpha v\beta 3$ blockade and its resultant effects on acute ischemic complications and restenosis after percutaneous transluminal coronary angiography remain to be determined.

Selected Abbreviations and Acronyms

FGN	= fibrinogen
ICAM-1	= intercellular adhesion molecule-1
mAb	= monoclonal antibody
TGF-ß1	= transforming growth factor-ß1

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References

Top
Abstract
Introduction
Methods
Results
Discussion
References

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Clinical significance of neutrophil adhesion molecules expression after coronary angioplasty on the development of restenosis.

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To investigate the neutrophil activation process following percutaneous transluminal coronary angioplasty (PTCA), we examined the expressions of Mac-1 (CD11b/CD18), L-selectin (CD62L), and sialyl-LewisX (SLX) on the surface of neutrophils after the PTCA procedure, by flow cytometric analysis. Twenty-nine patients with single vessel coronary artery disease of the left anterior descending artery who underwent elective PTCA were enrolled. In the 17 patients without restenosis at the follow-up angiography, the mean channel fluorescence intensity (MFI) for CD18, CD62L and SLX did not change after PTCA. Only the CD11b level was increased at 48 h after the PTCA. In the remaining 12 patients who developed restenosis, the MFI values for CD18 and CD11b were increased at 24 h and 48 h after the PTCA. The MFI value for CD62L was decreased and that for SLX was increased at 48 h after the PTCA. These changes were more prominent in the coronary sinus blood samples than in those of the peripheral blood samples. Our data indicate the down-regulation of L-selectin, probably by shedding, as well as the up-regulations of Mac-1 and sialyl-LewisX, especially in patients with restenosis. It is suggested that neutrophil activation by an interaction between the selectin family and carbohydrate ligands after PTCA may play a role in the development of restenosis, as does the integrin family.

Publication Types:
- Clinical Trial

PMID: 9459323 [PubMed - indexed for MEDLINE]

1: J Am Coll Cardiol 1997 May;29(6):1276-83

Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression. Evidence of inflammatory responses in coronary angioplasty.

Serrano CV Jr, Ramires JA, Venturinelli M, Arie S, D'Amico E, Zweier JL, Pileggi F, da Luz PL.

Heart Institute, School of Medicine, University of Sao Paulo, Brazil.

OBJECTIVES: This study sought to characterize leukocyte and platelet activation and adhesion molecule expression after coronary angioplasty. BACKGROUND: Coronary angioplasty can be regarded as a clinical model of postischemic inflammation because this intervention leads to the release of inflammatory mediators as a result of plaque rupture and endothelial injury. METHODS: In 13 patients with stable angina (mean [+/- SEM] age 56.0 +/- 2.4 years, range 44 to 79), blood samples were drawn from the aorta and coronary sinus immediately before and immediately and 15 min after coronary angioplasty. Subsequently, leukocyte and platelet functions were determined. Eleven control patients (57.5 +/- 2.3 years, range 52 to 78) underwent coronary arteriography. RESULTS: Coronary arteriography and angioplasty showed no difference in number of leukocytes between the coronary sinus and the aorta. However, 15 min after coronary angioplasty, there was an increase in neutrophil CD18 and CD11b, monocyte CD14 and platelet glycoprotein IIb/IIIa expression and a decrease in neutrophil L-selectin expression (189 +/- 25%, 163 +/- 27%, 158 +/- 35%, 141 +/- 22% and 31 +/- 10%, respectively, $p < 0.01$). In the control subjects, no change in adhesion molecule expression occurred. Superoxide production and aggregation in ex vivo-stimulated neutrophils collected from the coronary sinus 15 min after coronary angioplasty was significantly decreased compared with that after coronary arteriography (54 +/- 12% vs. 106 +/- 30% and 58 +/- 11% vs. 102 +/- 29%, respectively, $p < 0.01$). The reduced responses to phorbol ester stimulation may be explained by previous in vivo activation of neutrophils during coronary angioplasty. CONCLUSIONS: Coronary angioplasty increases neutrophil, monocyte and platelet adhesion molecule expression and induces a significant decrease in ex vivo-stimulated neutrophil superoxide generation and aggregation. These findings suggest that coronary angioplasty triggers cellular activation with an inflammatory response that could contribute to restenosis.

1: Thromb Haemost 1997 Apr;77(4):783-8

Inhibition of leucocyte and platelet adhesion reduces neointimal hyperplasia after arterial injury.

Golino P, Ambrosio G, Ragni M, Cirillo P, Esposito N, Willerson JT, Rothlein R, Petrucci L, Condorelli M, Chiariello M, Buja LM.

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Restenosis following coronary angioplasty is though to result from migration and proliferation of medial smooth muscle cells. However, the factors that initiate this proliferation are still unknown. In a rabbit model of carotid artery injury, we tested the hypothesis that activated platelets and leucocytes might contribute to the development of neointimal hyperplasia. Following arterial injury, rabbits received either no treatment, R15.7, a monoclonal antibody against the leucocyte CD11/CD18 adhesion complex, aurintricarboxylic acid (ATA), a substance that inhibits platelet glycoprotein Ib-von Willebrand factor interaction, or the combination of R15.7 and ATA. After 21 days, the extent of neointimal hyperplasia was evaluated by planimetry on histological arterial sections. The area of neointima averaged 0.51 +/- 0.07 mm2 in control animals and it was significantly reduced by administration of either R15.7 or ATA alone to 0.12 +/- 0.05 and 0.20 +/- 0.01 mm2, respectively ($p < 0.05$ vs controls for both groups). The animals that received the combination of R15.7 and ATA showed a further reduction in neointimal hyperplasia, as compared to animals that received ATA alone ($p < 0.05$ vs ATA alone). These data indicate that platelets and leucocytes play an important role in the pathophysiology of neointimal hyperplasia in this experimental model. Interventions that reduce platelet and leucocyte adhesion to vessel wall might have beneficial effects in reducing restenosis following coronary angioplasty.

PMID: 9134659 [PubMed - indexed for MEDLINE]

1: Am Surg 1995 Aug;61(8):674-9; discussion 679-80

Down regulation of CD11b and CD18 expression in atherosclerotic lesion-derived macrophages.

Gray JL, Shankar R.

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Monocyte/macrophages play an important role in the development of atherosclerosis. Electron microscopic evidence suggests that in the early stages, lipid laden monocytes leave the lesion to reenter the circulation. This reverse monocyte traffic ceases as the lesion develops. We hypothesize that monocyte/macrophages may not be able to exit the lesion and reenter the circulation because of the reduced expression of CD11/CD18 integrins. We have compared CD11b and CD18 expression of peripheral blood monocytes from normal rabbits (NMo) to atherosclerotic lesion-derived macrophages (AthMo) by anti-CD11b and anti-CD 18 antibody staining, followed by flow cytometry and immunohistochemical staining. AthMo were isolated from aortic lesions of rabbits fed 2 per cent cholesterol diet following balloon angioplasty. AthMo were separated into two regions based on their size and granularity by flow cytometry. All macrophages stained positively with RAM 11. Our results indicated that NMo showed a strong cell surface expression of CD11b and CD18. The less granular and smaller AthMo showed little anti-CD11b or anti-CD18 antibody staining, indicating very little CD11b or CD18 antibody staining, indicating very little CD11b or CD18 expression. The more granular and larger cells showed surface expression of both CD11b and CD18. With respect to CD18, over 90 per cent of NMo expressed CD18, only 37 per cent of the large granular AthMo and less than 1 per cent of the smaller, less granular AthMo stained positive for CD18. Immunohistochemical studies revealed strong surface expression of CD11b and CD18 on normal monocytes.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7618805 [PubMed - indexed for MEDLINE]

1: J Am Coll Cardiol 1996 Nov 1;28(5):1127-33

Expression of polymorphonuclear leukocyte adhesion molecules and its clinical significance in patients treated with percutaneous transluminal coronary angioplasty.

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Department of Cardiology, Koshigaya Hospital, Dokkyo University School of Medicine, Saitama, Japan.

OBJECTIVES: This study evaluated the role of neutrophil adhesion molecules LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18) and p150,95 (CD11c/CD18) in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). BACKGROUND: Several recent studies have suggested that cell adhesion molecules on both neutrophils and vascular endothelial cells play an important role in the process of tissue inflammation. METHODS: Thirty-eight patients (30 men, 8 women; mean [+/-SE] age 56 +/- 5 years, range 38 to 76) with single-vessel coronary artery disease of the left anterior descending artery underwent coronary angioplasty. Peripheral blood was sampled at baseline before, immediately after and 12, 24, 48 and 144 h after PTCA. The expression of CD18, CD11a, CD11b and CD11c on the surface of polymorphonuclear leukocytes was examined by flow cytometry with monoclonal antibodies. RESULTS: In patients without subsequent restenosis, there was no change in mean channel fluorescence intensity (MFI) of CD18 at each sampling time. However, in the patients with restenosis, the MFI of CD18 significantly increased at 48 h after PTCA (from 57 +/- 6 to 73 +/- 8, $p = 0.0008$). The MFI of CD11b increased slightly at 48 h after PTCA in patients without restenosis (from 584 +/- 121 to 735 +/- 114, $p = 0.037$). In patients with restenosis, the MFI of CD11b was slightly increased at 24 h after PTCA (from 586 +/- 122 to 768 +/- 214, $p = 0.018$) and significantly increased at 48 h after PTCA (to 1,534 +/- 268, $p = 0.0006$). The expression of CD11a and CD11c did not change at any sampling points after PTCA in either of the two patient groups. Percent change in the expression of CD18 at 48 h after PTCA (from baseline) and that of CD11b were correlated ($r = 0.73$, $p = 0.0008$) in patients with restenosis. CONCLUSIONS: Inflammatory stimuli within the coronary vessels associated with coronary angioplasty may upregulate Mac-1 expression on the surface of polymorphonuclear leukocytes. This process may be more marked in patients who experience later restenosis. Thus, activation of neutrophil adhesion molecule Mac-1 at 48 h after PTCA may have value as a predictor of subsequent restenosis.

1: Coron Artery Dis 1995 Sep;6(9):693-701

Role of leukocytes in neointimal formation after balloon angioplasty in the rabbit atherosclerotic model.

Guzman LA, Forudi F, Villa AE, Topol EJ.

Department of Cardiology, Cleveland Clinic Foundation, Ohio, USA.

BACKGROUND: Adherence and transendothelial migration of circulating leukocytes is one of the initial events after vascular injury. This process is mediated principally by the expression of integrins (CD11/C18) on the cell surface, which interact with their counterparts in the vessel wall cells. In order to determine the role of leukocytes in the development of neointimal thickening after balloon angioplasty, a monoclonal antibody (R15.7) against leukocyte adherence glycoprotein CD18 was used. METHODS: Femoral artery atherosclerotic lesions were induced in 20 New Zealand White rabbits, which were subjected to balloon angioplasty 28 days thereafter. Twelve hours before and 48 h after balloon angioplasty, 2 mg/kg body weight anti-CD18 or vehicle was randomly injected intravenously. Twenty-one days later the rabbits were killed and morphometric analysis performed. Measurement of functional activity of R15.7 in rabbit sera was performed, analyzing the capacity of the serum sample to inhibit aggregation of JY cells. RESULTS: The serum obtained from monoclonal antibody-treated rabbits showed more than 50% inhibition of cell aggregation at the time of balloon angioplasty. No effect on cell aggregation was seen in the sera of control rabbits. By angiography, there was no difference in lumen diameter and percentage stenosis at follow-up between the two groups. On morphometric analysis, there were no differences in the cross-sectional areas of intima, media, and lumen between the two treatment groups. The percentage cross-sectional area of intima was also similar in the two groups (0.672 +/- 0.04 versus 0.628 +/- 0.04). CONCLUSIONS: Blocking the CD18/CD11 glycoprotein pathway for leukocyte adhesion with a specific monoclonal antibody did not decrease the restenotic process after balloon angioplasty in the atherosclerotic rabbit arterial injury model.

PMID: 8747874 [PubMed - indexed for MEDLINE]

1: JAMA 1997 Aug 13;278(6):479-84 Related Articles, NEW Books, LinkOut

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- JAMA. 1997 Aug 13;278(6):518-9.
- JAMA. 1998 Jan 21;279(3):195-6.

Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication.

Topol EJ, Ferguson JJ, Weisman HF, Tcheng JE, Ellis SG, Kleiman NS, Ivanhoe RJ, Wang AL, Miller DP, Anderson KM, Califf RM.

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CONTEXT: Abciximab, a monoclonal antibody fragment against the platelet receptor alphaIIb beta3 integrin, prevents platelet aggregation. A randomized, placebo-controlled study showed that abciximab improves outcomes for patients undergoing percutaneous coronary angioplasty at 30 days and at 6 months. OBJECTIVE: To determine whether abciximab improves outcomes 3 years after coronary angioplasty. DESIGN: Double-blind, placebo-controlled, randomized trial. SETTING: A total of 56 academic and community hospitals in the United States. PATIENTS: A total of 2099 high-risk patients undergoing coronary angioplasty were randomized. Sufficient time elapsed for 2.5 years of follow-up among 2001 patients and for 3 years of follow-up among 1599 patients. INTERVENTIONS: Abciximab bolus of 0.25 mg/kg followed by infusion at 10 microg/min for 12 hours; abciximab bolus of 0.25 mg/kg followed by placebo infusion; or placebo bolus followed by placebo infusion. MAIN OUTCOMES MEASURES: The primary outcome was the composite of death, myocardial infarction, or coronary revascularization. Secondary outcomes were death, myocardial infarction, or coronary revascularization individually. Subgroups having refractory unstable angina or evolving myocardial infarction and having different elevations of creatine kinase during initial angioplasty were analyzed. RESULTS: At 3 years, composite end points occurred in 41.1% of those receiving abciximab bolus plus infusion; 47.4% of those receiving abciximab bolus only; and 47.2% of those receiving placebo only (for abciximab bolus plus infusion vs placebo, P=.009). Death occurred in 6.8%, 8.0%, and 8.6%, respectively (for abciximab bolus plus infusion vs placebo, P=.20); myocardial infarction in 10.7%, 12.2%, and 13.6%, respectively (for abciximab

bolus plus infusion vs placebo, P=.08); and revascularization in 34.8%, 38.6%, and 40.1%, respectively (for abciximab bolus plus infusion vs placebo, P=.02). Among those with refractory unstable angina or evolving myocardial infarction, death occurred in 5.1%, 9.2%, and 12.7%, respectively (for abciximab bolus plus infusion vs placebo, P=.01). Death rates increased as periprocedural creatine kinase levels increased. CONCLUSIONS: Abciximab bolus with infusion given at the time of coronary angioplasty improves outcomes as long as 3 years after the procedure.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9256222 [PubMed - indexed for MEDLINE]

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